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Herpes zoster after autologous hematopoietic stem cell transplantation

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ABSTRACT

Background: The autologous hematopoietic stem cell transplantation procedure involves immunosuppression of the patient. Thus, the patient has an elevated risk for several diseases, such as infections with the varicella-zoster virus. Prevention protocols have been proposed based on the use of acyclovir from the first day of conditioning, and maintaining this drug for 30–100 days after the procedure or for as much as one year. The objective of this work was to evaluate the incidence of herpes zoster after autologous transplantations related to the early suspension of acyclovir.

Methods: A retrospective study was carried out based on the collection of data from 231 medical records of transplant patients in the Bone Marrow Transplant Unit of the teaching hospital of the Universidade Federal de Juiz de Fora in the period between 2004 and 2014.

Results: Fourteen (6.1%) patients had herpes zoster in the post-transplant period on average within six months of the procedure. Patients with multiple myeloma (64.3%) were the most affected. There was a statistically significant difference in the age of the patients, with older individuals having a greater chance of developing the infection (p-value = 0.002). There were no significant differences for the other variables analyzed.

Conclusion: The early suspension of acyclovir can be safe in patients who receive autologous hematopoietic stem cell transplants. However some groups may benefit from extended prophylaxis with acyclovir, particularly older patients and patients with multiple myeloma.

Introduction

Autologous hematopoietic stem cell transplants (HSCT) are usually recommended as a recovery therapy for patients who receive myeloablative chemotherapy.[1] The immunosuppression caused by the conditioning leaves the patient at a high risk of acquiring different types of diseases. Infections are an important cause of morbidity in this process.[2] These patients therefore receive prophylactic medications, the most common of which are antibiotic, antiviral and antifungal agents.

Viruses, usually of the herpes family, such as the herpes simplex virus (HSV), cytomegalovirus (CMV) or varicella-zoster

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virus (VZV), are some of the most common causes of infections in the period after HSCT.[3]

Herpes zoster (HZ) is a painful vesicular eruption that is typically restricted to one or two dermatomes. It is the result of the reactivation of latent VZV virus in nervous ganglia, usually many years after the primary infection.[4] Infections caused by the varicella-zoster virus are quite common after HSCT, occurring in approximately 20–30% of patients submitted to autologous transplants within one year after transplantation.[4–6] Studies have shown that the occurrence of HZ is more common after the third month after transplant, with an incidence peak in the fourth month.[5]

The use of acyclovir as prophylaxis against the reactivation of herpes is considered standard care during neutropenia in autologous HSCT patients.[7] Different protocols include the prophylactic use of acyclovir on the first day of chemotherapy (conditioning), maintaining its use until Day 30–100 after HSCT in the absence of immunosuppression.[8]

In the Bone Marrow Transplant Unit of the Universidade Federal de Juiz de Fora (UFJF), the start of prophylaxis with acyclovir occurs on the first day of chemotherapy, and is suspended when the neutrophil count is greater than 500 cells/mm^3, i.e. when engraftment occurs, resulting in less time of use than recommended. The present study therefore aims to evaluate the incidence of infection by the herpes virus in patients submitted to autologous HSCT in respect to the early suspension of acyclovir.

Methods

This retrospective study compared the incidence of HZ in patients submitted to autologous HSCT with early interruption of prophylactic acyclovir compared to the usual scheme of one year reported in the literature.

The medical records of 221 patients submitted to HSCT in the period between 2004 and 2014 at the Bone Marrow Transplantation Unit of the UFJF, were analyzed retrospectively. Of these, nine patients underwent two transplants, totaling 230 procedures.

Data collection and variables

The data were collected from medical records. Data collection occurred in the period from March to September 2014. For the characterization of the population, data was collected related to gender, age, diagnosis, presence or absence of diabetes, in addition to the occurrence of death. Additionally, the occurrence of herpes before and after HSCT and other variables of interest were studied including the time of use of acyclovir, duration of neutropenia, length of hospitalization, use of corticosteroids or thalidomide after an outbreak of herpes, and the time of onset of the disease after the transplant. Although some records presented prior serology for HZ, many patients were not tested and thus the analysis of this variable was not performed.

All patients submitted to autologous BMT, independent of the baseline disease, received prophylactic acyclovir at a dose of 500 mg/m^2/day divided in 2–4 doses per day according to the period in which the procedure was performed. Prophylaxis was starting on the first day of conditioning and suspended when the neutrophil count was greater than 500 cells/mm^3.

After hospital discharge, the patients were monitored on an outpatient basis for a period of 24 months in the transplant service of the UFJF.

Data collection was only started after approval by the Research Ethics Committee of the UFJF (# CAAE 25735614.3.0000.5133).

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences software (version 19.0 for Windows). The Chi-square test was used for categorical variables and Student's *t*-test for numerical variables, means and medians. A p-value <0.05 was considered statistically significant.

Results

Two hundred and thirty medical records were analyzed. The mean age was 48.73 years (range: 4–79) and most patients were male (58.7%). The most commonly found diagnosis in the transplant service was multiple myeloma, totaling 52.2% of hospital admissions. The average length of hospital stay of the patients was 20.78 days. The characteristics of the population are described in Table 1.

Few patients had some type of associated comorbidity, with diabetes mellitus being the most common, occurring in 7.4% ($n = 17$) of the patients.

Eight patients (3.5%) had had HZ before hospitalization to perform the HSCT, only one of whom (0.43%) also presented HZ after the HSCT. Fourteen (6.1%) patients presented HZ after the HSCT; there were no significant differences in the evaluated variables between patients who had HZ after the HSCT and those that did not (Table 2). The average time of onset of the HZ outbreak was 164.6 days after the transplant (median: 144; range: 49–330 days).

Of the 14 patients who had HZ in the post-HSCT period, only one was taking corticosteroids/thalidomide during the onset of the infection (7.21%). Furthermore, only one patient

Table 1 – Characteristics of the population.

Variable	*n*	Percentage (%)
Gender		
Male	135	58.7
Female	95	41.3
Diagnosis		
Multiple myeloma	120	52.2
Lymphomas	97	42.2
Other diseases	13	5.7
Diabetes		
Presence	17	7.4
Absence	213	92.6
Death		
Yes	67	29.1
No	163	70.9

Table 2 – Occurrence of herpes after the autologous hematopoietic stem cell transplant and characteristics of the population.

Characteristics	Occurrence of herpes after HSCT				*p*-Value
	Yes	%	No	%	
Gender					
Female	3	21.1	92	42.6	0.119
Male	11	78.6	124	57.4	
Diagnosis					
Multiple myeloma	9	64.3	111	51.4	0.477
Lymphomas	5	35.7	92	42.6	
Other diseases	0	0	13	6.0	
Diabetes					
Yes	2	14.3	15	6.9	0.275
No	12	85.7	201	93.1	
Death					
Yes	2	14.3	65	30.1	0.289
No	12	85.7	151	69.9	
Total	14	100	217	100	

Table 3 – Occurrence of herpes after the autologous hematopoietic stem cell transplant regarding age, duration of acyclovir treatment and neutropenia.

Characteristics	Mean	*p*-Value
Age		
Herpes yes	57.14	0.001
Herpes no	48.19	
Prophylactic use of acyclovir in days		
Herpes yes	18.57	0.690
Herpes no	19.13	
Duration of neutropenia in days		
Herpes yes	8.82	0.350
Herpes no	9.15	

(7.21%) had a relapse of the disease. Moreover, one patient incurred the infection during mobilization, prior to HSCT. Most patients who developed HZ were patients with multiple myeloma (64.3%). Table 3 lists some characteristics related to the incidence of HZ.

A statistically significant difference was observed regarding the age of the patients who had herpes and those who did not develop it, with older patients having a higher likelihood of developing HZ. Considering only the patients with lymphoma or myeloma together with HZ, the difference in age was not significant; the first group had a mean age of 52.40 years and the second, 59.78 years (p-value = 0.233).

Discussion

The prophylactic use of acyclovir in the Bone Marrow transplant Unit of the UFJF starts on the first day of chemotherapy and ends when engraftment occurs. Fourteen patients (6.1%) had outbreaks of HZ after HSCT. Different protocols provide for the prophylactic use of acyclovir from the first day of chemotherapy (conditioning) to Day 30 or Day 100 after HSCT in the absence of immunosuppression, and possibly as long as one year of prophylaxis.[7,8]

However, there is insufficient evidence to strongly support the prolonged use of acyclovir in autologous HSCT, or to suggest that its effectiveness outweighs the potential adverse consequences.[5,9] Studies have reported that the continuous use of 400 mg/day of acyclovir until the end of immunosuppressive therapy may not suppress the reactivation of VZV after the discontinuation of acyclovir.[6] The prophylactic benefits should therefore be weighed against the toxicity, cost and risk of inducing resistance. In the analysis of allogeneic transplantations, however, the use of acyclovir for up to one year proved to be effective in the prevention of the reactivation of VZV.[6,8,10] In transplants performed using umbilical cord stem cells, an increased incidence of VZV was also demonstrated (46%) thereby justifying extended prophylaxis.[11]

Data from the literature demonstrated the probability of reactivation of VZV in 8.2% of the patients who received low prophylactic doses of acyclovir for one year.[12] In patients who did not receive acyclovir or who took it for a shorter period (until the end of neutropenia), the rates increased to 21–25%.[3,12] In the current study, 14 patients had outbreaks of HZ after HSCT, with an incidence of 6.1%, that is, a lower value than that found in the literature. This factor indicates that early suspension of acyclovir may be considered in stable patients. However, the present study has the limitation of being retrospective.

One study showed that the underlying disease might be a risk factor for the development of HZ. In a study conducted by Schuchter et al.,[3] the infection occurred mainly in patients with Hodgkin's or non-Hodgkin lymphoma (46%), compared with leukemia (20%) and solid tumors (9%), differing from this study, in which the greatest number of cases, albeit insignificant, occurred with patients with multiple myeloma (64.3%), followed by lymphoma (35.7%).

With respect to the age of the patients who incurred HZ, this study showed a statistical difference; HZ primarily affected patients with a more advanced age. This data is also demonstrated in another study, in which an age greater than 50 years was considered a risk factor for infection with VZV.[13]

The use of thalidomide has a potential immunosuppressive effect. One case study reported a disseminated infection caused by herpes simplex and an infection with VZV five years after autologous HSCT in a patient taking thalidomide.[14] In this study, however, only one of the patients who had HZ took this medication.

Although no serology is performed before the transplant, a prior history of HZ has a strong relationship with the positivity of the serologic testing.[15] In this specific case, only one of the eight patients who had had HZ prior to the transplant suffered a recurrence of the disease. This leads us to believe that performing serology for HZ before the HSCT may not be necessary, as this would indicate the extended use of acyclovir in patients with positive results.

New measures, such as vaccination against HZ, are being implemented. Previous studies have shown that the results of this measure may be negligible, since the vaccine is not recommended within the first year after transplant (live attenuated vaccine) and the incidence of VZV is rare after this period.[15] More recent studies, however, using immunization two months after HSCT with an adjuvant subunit of varicella-zoster virus glycoprotein E, have shown it to be a reasonable strategy to reduce HZ in autologous HSCT patients.[4]

Even though it was not in the scope of this article to assess the survival rate of patients, the mortality rate, regardless of its cause, was not influenced by the occurrence of HZ infection.

Although this work evaluated the records of 230 transplants, it was necessary to compare the data found with studies carried out in other institutions because this was a single center study. We conclude that the early suspension of acyclovir can be safe in low-risk patients submitted to autologous HSCT. This makes it possible to reduce not only the risk of resistance to medication, but the treatment costs. However, some groups may benefit from extended prophylaxis with acyclovir, particularly older patients and patients with multiple myeloma.

Conflicts of interest

The authors declare no conflicts of interest.

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